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Beta-blocker treatment in heart failure patients with atrial fibrillation: challenges and perspectives

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ABSTRACT Heart failure (HF) and atrial fibrillation (AF) are common conditions that share similar clinical phenotype and frequently coexist. The classification of HF in patients with preserved ejection fraction (> 50%, HFpEF), mid-range reduced EF (40%–49%, HFmrEF) and reduced EF (< 40%, HFrEF) are crucial for optimising the therapeutic approach, as each subgroup responds differently. Beta-blocker constitute an important component of our pharmacological regimen for chronic HF. Beta-blocker administration is reccomended in patients with HF with reduced ejection fraction in stable sinus rhythm, due to improvement of symptoms, the better long term-outcome and survival. The beneficial role of beta-blocker use in patients with preserved EF still remain unclear, as no treatment showed a positive impact, regarding morbidity or mortality reduction. The presence of AF in HF patients increases as the disease severity evolves and is associated with a higher rate of cardiovascular morbidity and mortality. But more question is the use of betablocker in HF patients irrespective of EF and concomitant AF. There are many conflicting data and publications, regarding the beta blocker benefit in this population. Generally, it is supported an attenuation of beta-blockers beneficial effect in HF patients with AF. A design of more randomised trials/studies with HF patients and concomitant AF may improve our clinical approach of beta-blockers use and identify the patients with HF, who mostly profit from an invasive approach.

Atrial fibrillation (AF) and heart failure (HF) with or without systolic dysfunction constitute common cardiac conditions, that frequently coexist and overlap.[1] These entities share multiple risk factors such as age, hypertension, diabetes, obesity, as well as cardiac substrates as valvular, ischemic, and non ischemic structural heart disease.[1, 2] Their coexistence can be partially explained by the presence of the common risk factors.[3]

The definition of heart failure revised in 2016, based on the measurement of left ventricular ejection fraction (EF).[4] Especially, HF can be divided in three groups: heart failure with preserved EF (> 50%, HFpEF), mid-range reduced EF (40%–49%, HFmrEF) and reduced EF (< 40%, HFrEF).[4] Interestingly, up to 50% of chronic HF patients present normal or only mildly impaired left ventricular EF.[5] The prevalence of AF in HF patients increases as the disease severity evolves.[6] Specifically, in patients with New York Heart Association (NYHA) I–II is typically about 5%, NYHA III approximately 26% and NYHA IV is presented up to 50%.[6] According to the data from randomized clinical trials and registries, the presence of AF in HFpEF patients ranges between 15% and 41%.[7] Patients with HFpEF are more likely to demonstrate prevalent AF or AF at any time up to twice, compared with those with HFrEF.[7] Data from the natiowide Swedish heart failure registry reported the prevelance of AF among LVEF ranges, specifically 53% in HFrEF, 60% HFmrEF, and 65% inHFpEF.[8] The presence of AF in HFrEF patients was 27% in an anaylsis of ESC-HF long term registry.[9] Notably, AF occurs in 24%–44% of patients in the setting of acute HF and in one third of those with chronic HF.[10, 11] Atrial fibrillation is also found in more than half (57%) of patients with new onset of HF.[12] Furthermore, HF is present in 33%, 44% and 56% of ambulatory patients with paroxysmal, persistent and permanent AF, respect-

ively and in more than one third (37%) of those with new onset AF.[12, 13]

PHENOTYPIC RANGE OF HEART FAILURE PATIENTS

The above HF classification is crucial, as each HF group demonstrates different underlying aetiologies, demographics, clinical phenotype, co-morbidities, response to therapies, all-cause and cardiovascular mortality, as well as HF hospitalizations. Patients with HFpEF tend to be older, more often women, with higher AF rates compared with HFrEF patients.[14, 15] On the contrary, HFpEF patients present less commonly a history of previous myocardial infarction.[16] Notably, patients with HFmrEF demonstrate similar characteristics such as age, ischemic heart disease (IHD) to patients with HFrEF and HFpEF.[17] The baseline co-morbidities such as hypertension, diabetes, and AF are more frequent presented in patients with HFmrEF than in those with HFrEF but less frequently in patients with HFpEF.[17] In conclusion, HFmrEF category seem to display a position between the two previous established categories.[17]

It should not be understimated that the prognosis of HFpEF patients remains poor and is almost similar to that of HFrEF patients.[18] Cardiovascular mortality seem to be lower in HFmrEF than in both HFrEF and HFpEFpatients.[19] The higher prevalence of IHD and reduced LVEF in HFrEF and the higher incidence of hypertension, diabetes, and AF in HFpEF patients may also explain partially the higher cardiovascular mortality in these two categories in comparison to HFmrEF.[20]

IMPACT OF ATRIAL FIBRILLATION IN HEART FAILURE PATIENTS

AF has an adverse impact on cardiac function deterioration via multiple pathways, such as loss of atrioventricular synchrony, reduced filling time, decreased ejection time and stroke volume in the context of tachycardia and a greater prevalence of right and left biventricular performance impairment.[21] Nevertheless, a condition known as tachycardia-induced cardiomyopathy is evident in 25% to 50% of patients with left ventricular dysfunction and AF.[22, 23] On the other hand, AF remains the most common cause of tachycardia-induced cardiomyopathy.[24, 25] The restoration of sinus rhythm (SR) or appropriate rate control, achieving the elimination of these rapid heart rates, reverses the hemodynamic and clinical manifestations associated with this syndrome.[26, 27] Similarly, HF can increase the risk of AF development in several ways, including elevation of cardiac filling pressures, electrical remodelling, strucutural alterations with interstitial fibrosis, dysregulation of intracellular calcium, autonomic and neuroendocrine deregulation.[28] Both clinical entities trigger increased mechanical cardiac stress, electrical remodeling and inflammation, leading to cardiac hypertrophy/fibrosis and shortening of the atrial effective refractory period, sequences that support the hypothesis that AF and HF constitute a vicious cycle.[28–30]

Generally, the presence of AF is associated with a higher rate of cardiovascular morbidity and mortality in symptomatic patients with HFrEF or HFpEF, attributable to co-existing AF.[31] The stroke risk seems almost equal in both groups.[31] New onset of AF in HF patients increased significantly the cardiovascular mortality, hospitalisation, fatal and non-fatal stroke, as reported in Charm-Study.[32] Similar results revealed the Comet- and Valiant-studies regarding the relationship of AF adverse events in HF patients.[33, 34] Verma, *et al* supported, that the coexistence of AF and HF were associated with increased rate of stroke, hospitalization and all-cause mortality.[35] Previous studies demonstrated that the incidence of non-cardiac related hospitalizations in HFpEF was much higher, while the incidence of HF-hospitalizations in HFpEF was lower compared to HFrEF.[36, 37] Furthermore, the group of patients with HFpEF and the presence of AF in the TOPCAT trial was related with a significant increase in the risk for cardiovascular mortality, HF hospitalization, and all-cause mortality compared with patients without AF.[38] Notably, in this study new onset AF in HFpEF patients after enrollment was related with an especially high morbidity and mortality risk (i.e., a 2.2-fold increase in risk in those with either no history of AF or history of AF who were not in AF.[39, 40] Both RELAX- and Lam Study showed that HFpEF patients with AF had poorer exercise capacity, higher NT-proBNP levels, and more dilated left atria compared with those in SR.[41, 42]

All the above findings suggested a more advanced HF stage in patients with coexistence of AF and HF, while HF patients with new onset AF demonstrate worse prognosis regarding cardiovascular outcomes and events.[43]

BETA-BLOCKER TREATMENT IN PATIENTS WITH HFREF AND SINUS RHYTHM

The treatment of patients with AF and HF is crucial aiming at the reduction of cardiovascular events and mortality. Current guidelines recommend beta-blockers' administration in patients with HF irrespective of rhythm disorders. The beta-blockers constitute the cornerstone therapy of patients with HFrEF and stable SR (Class I, Level Evidence: A).[44] The MOCHA investigators reported that beta-blockers (BBs) resulted in a dose-dependent improvement of left ventricular function and decrease in mortality and hospitalization rates in HF patients with reduced EF (HFrEF).[45] Moreover, in CAPRICORN study, beta-blocker therapy has been shown to prevent new onset or recurrent AF in HF patients with impaired left ventricular function after myocardial infarction (5.4% in placebo *vs.* 2.3% in beta-blocker group), after a mean of 1.3 years, and also in a relatively low-risk mostly hypertensive population.[46]

Overall, a systematic review of Imad Abi Nasr *et al* including different types of beta-blocker (CAPRICORN with carvedilol,[46] CIBIS I with bisoprolol,[47] MERIT HF with metoprolol,[48] BEST bucindolol,[49] COPERNICUS with carvedilol,[50] Waagstein with metoprolol,[51] Seniors with Nebivolol,[52] showed a clear reduction in incidence of new AF in patients with HFrEF from 39 to 28 per 1 000 patient-years (relative risk reduction 27%; 95% CI: 14–38, $P < 0.001$).[53] The only exception was the Seniors study associated with no significant reduction of new onset AF in Nebivolol group, fact that may partly be attributed to study design, included elderly patients with higher prevalenceof AF at randomisation, and higher proportion (one-third) of HFpEF patients.[53] Clinical trials have shown, that the adminstration of carvedilol, bisoprolol and metoprolol improved survival and reduced cardiac hospitalIzations in patients with HFrEF, while nebivolol presented a reduction of cardiovascular hospital admissions but no effect on mortality.[53, 54] Also, the above studies revealed a significant reduction of sudden cardiac–heart failure death and HF hospitalization.[53, 54] Furthermore, in the Copernicus study patients with more advanced HF with LVEF under 25% and NYHA IV, demonstrated a benefit also from Carvedilol treatment with 35% mortaliy risk reduction, despite the terminal stage of HF.[55] The benefits of beta-blocker administartion and the improvement of survival seem to be dose-related (higher dose better outcomes compared to medium/low dose).[56] Stefania Paolillo supported the theory, that the positive beta-blocker effects were also dependent on heart rate reduction, as demonstrated in the Shift study.[57, 58] The beneficial role of beta-blockers treatment reflected on a composite outcome of CV death, urgent heart transplantation, or LVAD implantation.[58] Chatterjee, *et al.* and Paolillo, *et al.* observed no differences between selective and non-selective -blockers on outcome, although carvedilol demonstrated a tendency on mortality reduction compared with the other beta-blockers.[58, 59] Another meta-analysis comparing the effects of carvedilol to metoprolol on LVEF in HF patients revealed that carvedilol lead to greater improvement on LVEF than metoprolol at similar doses.[60] Beta-blockers in patients with HFrEF and advanced CKD were independently related with reduced mortality similar as in HFrEF with moderate CKD.[61] However, the above beneficial role of betablocker was not presented in patients with HFpEF or HFmrEF with severe CKD and in patients in HFrEF and atrial fibrillation.[61]

In conclusion, there is no doubt of the beneficial impact of beta-blocker treatment in patients with HFrEF and SR.

BETA-BLOCKER TREATMENT INPATIENTS WITH HFREF AND ATRIAL FIBRILLATION

The majority of HF patients included in the above clinical trials with BBs were in SR, with only a minor portion of patients with AF, ranged between 11% to 35%.[62]

It remains unclear, if BBs could prevent HF progress and cardiovascular events in patients with AF. There are several hypothesis supported, that the beta-blocker treatment is less effective in HF pa-

tients with AF than in those with SR.[63] In SR BBs act to the sinus node, but in AF these agents target the atrioventricular node.[63, 64] Also, the heart rate drop is different during rest and exercise between patients in AF and SR.[64] In AF patients with loss of atrial contraction, a higher heart frequency may be needed to achieve an adequate cardiac output.[64, 65] So it is possible, that the uptitration of beta-blockers 'dose could result in an aggresive heart rate reduction, worsening the underlying HF.[65] Furthermore, a low heart rate under beta-blocker, especially in elderly patients with AF, may unmask an underlying conduction system disorder.[66, 67] AF in patients with HF may constitute a marker of a poorer clinical condition and a sign of a more advanced disease, leading to a worse outcome, less modificiable by beta-blocker treatment.[68] The controversial effect of beta-blockers, regarding survival, mentioned also in the AF treatment guidelines of 2016, where beta-blockers are recommended as a rate control approach in order to reduce the AF-related symptoms but not to improve prognosis.[69] The effect of beta-blockers on outcome in AF patients with HFrEF is reduced compared to those with SR.[69] A subgroup analysis of the four randomized placebo–controlled studies (USCS, MERIT-HF, CIBIS II, Seniors) focused on patients with AF and reduced EF, revealed that beta-blockers did not achieve a positive effect on HF hospitalizations (odds ratio [OR] = 1.11; 95% CI: 0.85–1.47; P = 0.44), or mortality (OR = 0.86; 95% CI: 0.66–1.13; P = 0.28) in comparison to patients with SR.[70] Similarly, Cullington, *et al* demonstrated that a slower resting ventricular rate is associated with better survival in HFrEFpatients in SR but not in AF patients.[71]

Kotecha, *et al*.[72] analyzed data from 10 randomized controlled trials of 18,254 symptomatic patients with HFrEF treated with beta-blockers versus placebo, 26.8% of whom were presented with AF. The BBs treated group was associated with significantly lower mortality in patients with SR (HR = 0.73; 95% confidence interval [CI]: 0.67–0.80; P < 0.001) but not in AF (HR = 0.97; 95%CI 0.83–1.14; P = 0.73).[72] The investigators concluded that beta-blockers "should not be used preferentially over other rate-control medications and not regarded as standard therapy to improve prognosis in patients with concomitant HF and AF.[72] Although, there was a trend of beneficial effect in beta-blockers treatment when the composite endpoint of death or hospitalisation was analysed (HR = 0.89, P = 0.06).[72]

On the contrary, beta-blockers were associated with significant reduction on all cause mortality (28%) but not hospitalisation or cardiovascular mortality in HFrEF patients and coexisting AF, according to AF-CHF Study propensity-matched sub-analyses.[73] The positive impact of beta-blockers was consistent regardless of the AF type or duration (paroxysmal *vs.* persistent, high vs slow).[73] Whereas, the high rate of hospitalizations for AF overall (i.e., 20%) might reflect the AF-CHF trial design, based on an aggressive approach to maintain SR.[73] However, the AF-CHF subgroup study displays also limitations as it was not a randomized comparison, and the potential for confounding exists.[73] Same results reported also in the Swedish Heart Failure Registry and in a nationwide cohort study with 29% and 25% reduction of mortality, respectively.[74, 75]

The above results are different in comparison with the respective by Kotecha and Rienstra.[70, 72–75] The conflicting results may be partly explained by differences in methodology, patient demographics, HF stage and type, medications (beta-blocker type-or target dose), heart rate target or follow-up duration. Overall, given the heterogenous nature of different studies, no firm conclusions can be drawn regarding b-blockade impact in AF patients with HFrEF.

Especially, Kotecha publication was criticized as only a single electrocardiogram was used to classify baseline patient rhythm. Thus, many of the patients with SR potentially had paroxysmal AF. The low reported prevalence of AF (17%) in a population with HFrEF was consistent with a potential misclassification error, as this percentage was much lower than the prevalence of AF (41%) in HF patients from the swedish registry.[72, 74] In addition, Kotecha's study included patiens with more advanced HF stage, receiving more diuretics and aldosterone antagonists, with a prevalence of NYHA functional class III or IV symptoms about 70% vs. 30% of respective patients in the AF-CHF study.[72, 73] While in the Swedish HF-registry, about 50% patients presented with NYHA class I/II HF stage.[74]

Furthermore, only 58% of patiens in Kotecha's study received oral anticoagulants in comparison to AF-CHF study, where up to 82% were under oral

anticoagulation.[72, 73] Another difference was the higher proportion of patients on digoxin therapy in the study of Kotecha (83%) in comparison to AF-CHF and Swedish HF-study 65% and 36%, respectively.[72–74] In Kotecha's study, a more aggresive beta-blocker target dose was observed, as 72,1% were on maximal dose of beta-blockers *vs*. 28% of patients in Swedish HF-study.[72, 74] Another point is that Kotecha's study enrolled stable or patients with permanent AF in comparison to Peter Brønnum Nielsen Nationwide Cohort Study's in Denkmark, that included patients with a first-time hospital AF diagnosis, showing a mortality reduction with beta-blocker therapy in AF patients with concomitant HF.[72, 75] It has been previously mentioned that new onset AF in HF patients is associated with higher mortality rates, explaining partially the positive effect of beta-blocker treatment in survival in new onset AF patients in contrast with permanent AF patients.[72, 75] It is widely known that the combination of beta-blocker and digoxin has controversial effects based on the published data.[76]Digoxin is adminstrated mainly in erdely and frailer AF patients with more neutral longterm outcome as in SCAF study (The Stockholm Cohort of Atrial Fibrillation SCAF study).[77] The Registry of Information beta-blockers, digoxin and atrial fibrillation and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA) showed a higher overall mortality in digoxin-treated patients with AF without coexisting HF, but not a great difference in patients with HF.[78]A sub-analysis of AFFIRM trial reported that AF patients under digoxin had higher all-cause mortality after adjustment for comorbidities and propensity scores, regardless of the presence or absence of underlying HF.[79] Whereas, another *post-hoc* analysis from the AFFIRM study demonstrated that digoxin can provide benefits in HFrEF patients with AF.[80] Furthermore, beta-blocker alone or in combination with digoxin irrespective of AF burden (permanent or non) or HF phenotype (preserved or reduced LVEF) associated with neutral and no worse survival compared with a rate control strategy.[81] Similarly, in a recent meta-analysis of observational and controlled data digoxin was associated with a neutral effect on survival and a lower rate of hospitalisation.[82] It still remains not well defined, whether dixogin treatment in combination with beta-blocker or not, may play a beneficial role as rate control therapy and if the AF profile (permanent or non-permanent), or HF type (HFrEF or HFpEF, ischaemic or non-ischaemic aetiology) can further affect its action. The potential interaction between beta-blocker and digoxin in patients with mild chronic kidney disease, might also have resulted in the lack of beta-blockers beneficial effect in patients with HF and AF.[83]

The effect of beta-blockers' treatment on heart rate variation should also be taken into account. In Li's study a heart rate > 100 beats/min was associated with increased mortality in all HF patients with AF.[84, 85] The enrolled patients in Kotecha's study had a median heart rate of 81 beats/min, giving more neutral results and possibly underestimating the beneficial effect of beta-blockers' treatment driven by a strict heart rate lowering target under 100 beats/min.[72, 85]

In conclusion, the more advanced HF, the neutral effect due to digoxin use, the underprescription of anticoagulation, the higher betablocker dose might have attenuated any benefits of beta-blockers on mortality in HF patients with AF.

BETA-BLOCKER THERAPY IN PATIENTS WITH HFPEF AND ATRIAL FIBRILLATION

Generally, HFpEF patients constitute an heterogenous group with various phenotypes and comorbidities, and further difficulty of the identification of patients, who will benefit from betablocker medical treatment.[86]

A doubt of a positive impact of betablocker administration in HFpEF patients still remain.[87, 88]No treatment has yet been proven to reduce morbidity or mortality in patients with HFpEF or HFmrEF.[87, 88] The optimize HF registry failed to identify a prognostic effect of BBs use in this special population.[89] Clenand, *et al*.[90] also reported an improvemet of LVEF and all cause and cardiovascular mortality reduction in SR patients with HFmrEF and HFrEF, but not a statistically significant effect in HFpEF patients with SR. The lower the LVEF, the higher the benefit of BBs.[90] The above groups with coexistence of AF had a better LVEF but this failed to be translated into a better outcome.[90] The population with AF and either HFrEF or HFmrEF expierienced

an LVEF improvement without benefit on prognosis. Interestingly, no benefit was seen in patients with preserved LVEF > 50% in SR or AF.[90]

High heart rate predicts poor outcomes in patients with HFpEF and SR. Especially, each standard deviation (12.4 beats/min) increase in heart rate was associated with an 13% increase in risk of cardiovascular death or HF hospitalization (P = 0.002), fact that does not apply in AF.[91] Indeed, in I-PRESERVE study, no correlation was observed in HFpEF patients with AF between heart rate and outcomes. Also, beta-blocker administration did not change the heart rate-risk relationship in patients with HFpEF independent of rhythm.[91] Another study showed that, in patients with HFpEF and SR with a heart rate ≥ 70 beats/min, high dose of beta-blockers was associated with a significantly lower risk of death.[92]

Some observational studies demonstrated, that beta-blocker treatment decreased the all-causemortality risk in the HFpEF patients with AF or SR.[93, 94] the fact that was not observed in the sub-analysis of SENIORS trial and J DHF trial.[95, 96] A possible explanation of beneficial beta-blocker effect in HFpEF population, might be mainly due to the antihypertensive effect, the arrhythmic-risk reduction, the myocardial perfusion and metabolism improvement, as well as ventricular remodeling, and any protection against acute coronary events.[97] Despite the possible all cause mortality reduction, the lack of hospitalizations' reduction is probably due to the fact that the patients with HFpEF tended to be elderly and with multiple non-cardiac or/and cardiac comorbidities.[97] Another meta-analysis demonstrated the benefit of the use of beta-blockers for all-cause mortality, but not for HF by beta-blocker use in patients with HFpEF and SR or AF.[98] Although evidence for the benefits of beta-blocker therapy in-HFpEF patients is lacking, these agents are used usually for comorbidities' management such as hypertension, coronary artery disease and AF.

A meta-regression analysis of randomized controlled trials underlined the beneficial role of beta-blockers in HFpEF with coexistence of CAD or AF in a small number of patients.[99] The above subgroup of patients demonstrated lower BNP levels and an increase of exercise capacity on beta-blocker therapy compared to HFpEF with neither CAD or AF treated with betablocker. The use of beta-blockers in HFpEF in patients with AF or CAD should be well balanced between potential benefits and adverse events.[99] On the one hand, beta-blockers provide a reduction of left ventricular oxygen consumption and myocardial perfusion improvement via the negative chronotropic action, but on the other side the unmasking of any conduction disorders or chronotropic intorelance may negatively influence this subgroup of patients.[99] The definition of this narrow therapeutic range/window of beta-blocker effect remains challenging.

The beta-blocker therapy in HFpEF patients with AF according to the retrospective clinical study of Yang, resulted in a significantly lower mortality and a slight increase of the rehospitalization risk due to worsening of HF, post exclusion of patients with severe comorbidities compared with those without beta-blocker treatment.[100] The above analysis offered a better understanding of beta-blocker effect on HFpEF patients with AF but without other comorbidites.[100]Another subgroup analysis of patients with HFpEF and AF (30% of the whole population) in a Korean registry showed that the beta-blocker treatment has eventually a beneficial role with regard to efficacy.[101]

It shoud be highlighted that the majority of meta-analysis or studies enrolled patients with stable HFpEF. Another interesting point was the effect of beta-blockers in acute setting of HFpEF and AF.[102] Min-Soo Ahn reported a reduced rehospitalization rate in 639 patients with acute HFpEF and AF during the 6-month and 1-year follow up.[102] Furthermore, ACE-inhibitors or/angiotensin receptor blockers (ARBs), statins and beta-blockers alone or in combination can play a protective role in development of HFpEF among patients with AF.[103] Beneficial effects of betablocker may be present in selected subclasses of patients with HFpEF and AF. Further studies are required to identify those groups.

RATE CONTROL IN HEART FAILURE PATIENTS WITH SINUS RHYTHM OR ATRIAL FIBRILLATION

Resting heart rate is an important predictor of outcome in patients with stable HFrEF and SR.[104] Generally, a lower heart rate is associated with bet-

ter outcomes in this patient population. The magnitude of heart rate reduction with beta-blocker usage, but not beta-blocker dose in SR patients was associated with a survival benefit.[105] But the above positive impact of beta-blocker-use remains unclear and controversial in patients with HFpEF and SR. Using Propensity score-matched patients and data from Optimise study, a heart rate < 70 beats/min at discharge of patients with HFpEF, showed a significantly lower risk of the composite end point of HF readmissions or all-cause mortality, but not of either HF or all-cause readmissions individually, compared with those with a heart rate above 70 beats/min.[106] Another interesting point was that a discharge prescription of beta-blockers or other heart rate-lowering drugs in a subgroup of patients presented with coronary artery disease, prior myocardial infarction and coronary revascularization might be beneficial.[107]

Patients with HFrEFor HFpEF and AF consist a more complex field of beta-blocker impact. Van Gelder *et al*.[108] demonstrated that in AF patients, with or without HF, the lower heart rate is not associated with a better outcome. On the contrary, beta-blockers may both control the ventricular response of AF and improve survival in patients with HF and concomitant AF based on a small retrospective analysis of the US Carvedilol Heart Failure Trial, revealing a trend toward a reduction in the combined end point of death or CHF hospitalization in carvedilol treated patients compared with placebo (RR = 0.35; 95% CI: 0.12–1.02; P = 0.055).[109]

An intensive heart rate control was proven difficult in patients with chronic AF and HFrEF due to patient intolerance of increasing doses of betablockade, and it was not associated with improved outcomes.[110] Similarly to the study by van Gelder and colleagues, an aggressive rate control in patients with chronic AF and HF did not add any benefit.[111] The RACE II-Study evaluated the lenient versus strict rate Control in permanent AF-patients, and showed that lenient rate control (defined as resting HR control < 110 beats/min) led to similar outcomes, regarding cumulative incidence of death from cardiovascular causes, hospitalization for HF, thromboembolic events, bleeding and lifethreatening arrhythmia; as strict rate control (defined as resting HR control < 80 beats/minute).[111] It should be emphasized that the majority of patients enrolled in RACE II study demonstrated a mean ejection fraction (EF) of 52%, while patients with an EF < 40% presented only 15% of the total population.[111] It is obvious that the study revealed no benefit of strict rate control in patients with preserved ejection and AF.[111]

In a second prospective randomised study of ibopamine's effect on Mortality and efficacy study, HFrEF patients and AF with mean ventricular rate > 80 beats/min presented better outcomes than those with < 72 beats/min.[112] On the same line, Cullington, *et al*.[113] showed a worse survival in HF patients with AF and ventricular rate < 73/min. Especially, AF or SR patients had a similar prognosis, despite substantially higher ventricular rates in AF patient.

A study of Miller, *et al* [114] found no relationship between predischarge heart rate or BBs dose/titrating dose in patients with recent hospitalisation for HF with reduced or preserved LVEF and AF, suggesting a more lenient rate control goal with no obvious effect of beta-blocker adminstration.

The optimal resting ventricular rate in patients with AF and HF is uncertain but may be ranged between 60–100 beats/min. AF ESC guidelines of 2016 and 2020 recommend a resting ventricular rate of up to 110 beats/min as the target for rate control therapy independent of HF.[115, 116] However, the Task Force and the guidelines of ESC-HF support that a lower rate for patients with HF may be preferable (60–100 beats/min), specifically 60–100 beats/min at rest and < 100 beats/min at exercise.[117] The updated 2011 American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society (HRS) guidelines for management of AF recommend a strict HR control for patients with both conditions, with a HR goal of 60 to 80 beats/min at rest and 90 to 115 beats/min during moderate exercise, even though there are few outcomes/data to support that recommendation.[118] The 2009 ACC/AHA guidelines for management of HF advocate a somewhat more lenient approach, with the HR goal of < 80 to 90 beats/min at rest and < 110 to 130 beats/min during moderate exercise.[119] The above recommendations lead to conflicting evidence regarding the optimal heart rate target in patients with AF and HF.

The optimal heart rate of beta-blocker driven therapy should be for each HF patient with AF indivualised, taking into account the heart size, cardiac systolic and diastolic function and the concomitant valve function and any underlying comorbities.[120]

RHYTM CONTROL

A plethora of studies (PIAF, STAF, RACE, HOT CAFE and AFFIRM) demonstrated no superiority of rhythm control against rate control approach, irrespective of EF and mostly in underpowered HF population.[121–125] Besides, a meta-analysis documented a 17% increase in the risk of hospitalisation in the rhythm control group, but it must be highlighted the significant heterogeneity of the studies.[121–127]

AFFIRM study demonstrated no survival advantage in rhythm-control approach of AF patients over the rate-control strategy, however the patients with HF presented only 23.1%, and about 9% had an NYHA functional class of II or greater.[128, 129] LV function was normal in 76% of AFFIRM patients.[128, 129] In the subgroup analysis, a trend was found for positive impact of rhythm control strategy in patients suffering from HF, but statistically not significant. It must be highlighted, that SR was maintained in only 63% of patients in the rhythm control arm of AFFIRM in a period of 5 years, that may be the reason for the benefit attenuation of this approach.[128, 129]

The AF-CHF study was the first prospective randomized study to assess the effect of rate versus rhythm control in HF patients.[129, 130] A total of 1376 patients, with AF and HFrEF (mean LVEF, 27%) were enrolled and randomized to rhythm control (typically with amiodarone) versus rate control in a mean follow-up of 3 years.[130] The rhythm control group did not improve mortality, heart failure hospitalization, or stroke compared with rate control.[130] Another recent subanalysis of the RACE study in patients with AF and mild to moderate HF supported also that rate control was not inferior to rhythm control in the prevention of a combined end point of morbidity and mortality during 2.3 years of follow-up.[131]Another large study of 1,009 patients with moderate to severe left ventricular dysfunction and AF similarly demonstrated no benefit on overall mortality of rhythm compared with rate control.[132]

However, a subgroup analysis of Diamond study showed that the SR restoration was associated with a significant higher survival rate in patients with AF or atrial flutter and EF < 35%.[133] These findings, support the theory, that the rhythm control and SR restoration could be more beneficial in patients with more advanced NYHA stage and more significant LV function impairement (LVEF < 35%) in comparison with mild to moderate HF patients.[133]

The randomized Castle AF trial in patients with AF and significant HFrEF demonstrated a better outcome in the risk of all cause death or hospitalization and LVEF improvement of ablation compared with medical therapy (rhythm vs rate control).[134] Also, in a prespecified subgroup analysis of CABANA trial exhibited a non significant trend on primary endpoint reduction among AF patients with a history of HF.[135, 136] It is crucial to identify HF patients with factors such as non ischemic aetiology cardiomyopathy, LVEF > 35% and limited extension of atrial fibrosis of 10% or less, who may be the mainly responders of AF ablation.[134–138] Cabana and Castle AF emphasized that patients with HFrEF may benefit from ablation, leading to a AF burden reduction, improvement of LVEF and lower toxicity effect in comparison to medical therapy.[138, 139]

Recently, the AMICA trial studied also patients with more advaced HF compared to Castle AF study and persistent AF who underwent catheter ablation or remained only in optimal medical therapy.[140] The invasive approach showed a similar improvement of EF in one year follow up as in the medical group and no significant benefit of ablation.[140] AF-Ablation is not imperative in all HFrEF patients, taking into consideration the result of AMICA trial and also the neutral effect of ablation by subgroup analyses of the primary end point in CASTLE-AF in patients with NYHA III HF symptoms as well as in patients with an LVEF< 25%,who did not show any benefit.[134–136, 140]

CONCLUSION

The adminstration of beta-blockers in HF patients with AF is not well defined. There are many questions and controversial data regarding their beneficial effect in this population. Are the type or dose of beta-blocker crucial for a better patients' outcome? Which is the optimal heart rate target in

this specific population? Are the advantages of beta-blocker use dependent on EF (reduced vs preserved)? Is it any association of beta-blocker and HF type and severity (for example in extreme low LVEF or reduced right ventricular function, and concominant valve failure)? Should be used as first line rate control in HF-AF patients? Are specific subgroups of HF-AF patients and comorbidities, who mostly may benefit? The combined treatment of beta-blocker with digoxin or amiodarone can affect the patient prognosis? Is there a favourable outcome of AF ablation in combination or not with beta-blocker vs medical treatment alone?

We need more randomised trials/studies to improve our clinical approach of beta-blockers' use in heart failure patients accompanied with AF. This is the only way to achieve an evidence based beta-blocker administration, achieving an individual targeted therapy with better outcomes and lower adverse/side effects.

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